REMARKS

The Applicants appreciate the Examiner's thorough examination of the subject application. Applicants request reconsideration of the subject application based on the following remarks.

Claims 284-286 and 288 are currently pending in the application. Claims 284-286 and 288 have not been amended and no new matter has been added to the specification or the claims.

More particularly, in the currently outstanding Official Action:

1. Claims 284-286 and 288 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, as set forth in the previous Office action. The claims contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that Applicant, at the time the application was filed, had possession of the claimed invention.

> The Examiner states, "Applicant's arguments filed March 6, 2006 have been fully considered but they are not persuasive. It appears to be Applicant's position that the examples presented in the specification provide the written description of the generic compositions. Applicant cites the example of patient 1 "who received DMSO a chemotherapeutic agent [component 1(i)], hyaluronic acid [component 1(ii)] followed by hyaluronic acid [component 2(i)] and indomethacin[component 29ii)]." First of all, it is not clear how in this context DMSO could be extrapolated to describe the genus "chemotherapeutic agents," when the specification describes DMSO as a "penetration enhancer" or a treatment for edema.
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> The examiner agrees that the specification present "dozens of examples," 40 examples, in fact, and Applicant provides a table indicating how 28 of these 40 examples allegedly apply to the claims. It is noted that Applicant admits that eight of those 28 are *not applicable to the claims*. It is the examiner's position that not only do the examples not provide adequate written description for the claimed genus, several of the examples that Applicant deems descriptive, are not even consistent with the limitations of the claims. For example, at a minimum the claims require two dosage amounts of [some agent] in combination with HA

wherein the two dosage amounts are not the same. Take Case X, for example. This patient is treated with "low dose chemotherapy and the carrier/penetrating molecule, hyaluronic acid." There is no indication of two different dosage amounts. The same is true for Case XVII. The examiner maintains that there is no clear guidance in the specification that leads one to the claimed generic compositions or any indication that Applicant had possession of said generic compositions.

With respect to claim 288, Applicant states in the table that the treatments for patient 9 and patient 17 are applicable, possibly because these are the only examples that use novantrone. However, it is not clear how these examples describe a composition comprising diclofenac.".

The applicant respectfully submits that the specification clearly provides support for the claims as defined in the instant application as follows.

The Examiner rejects the claims because there is no support for a pharmaceutical composition comprising a chemotherapeutic agent, and wherein the dosage amounts are not the same.

Applicant in an earlier submission argued that the examples presented in the specification provide the written description of the generic compositions. In one of the examples, Patient 1 "received DMSO a chemotherapeutic agent, HA followed by HA again and indomethacin".

The Examiner rejected this submission alleging it was not clear how DMSO could be extrapolated to describe the genus "chemotherapeutic agents", when the specification describes DMSO as a "penetration enhancer" or a treatment for edema.

Reference to DMSO within the specification and in prior correspondence may have resulted in some confusion. DMSO is acknowledged as a carrier/ penetration agent (*para* 142; 179). Examples of certain drugs and drug combinations with DMSO are provided in the specification (see, for example, Cases I, III, LXXXII). These examples are provided to contrast the effect of the same drugs / drug combinations with HA. The earlier response to 112 rejection does not rely on the use of DMSO as a drug.

Case II describes treatment of a patient (who had developed malignant melanoma with tumour present in the inguinal nodes) first by intravenous (ie, systemic) administration compositions comprising phloretin together with HA at a dose of 10 to 50mg; and via systemic therapy with carboplatinum (250 mg) with HA; plus orally, methyl CCNU (120mg) while the patient received HA systemically. Methoxtrexate (37.5 mg) mixed with HA (60 mg) was also injected into the tumour. Hence the specification describes to the skilled addressee in the art a pharmaceutical composition comprising as a **first** component for systemic administration a formulation comprising HA and phloretin (chemotherapeutic agent), and alternatively HA with carboplatinum ; and administration by injection of a **second** component a formulation comprising of HA and methoxtrexate as the anti-cancer agent. Furthermore, clearly the dosage amounts administered to the patient for the two components, ie, via systemic administration or by injection, are different, and not the same, as indicated above.

Thus Case II provides support in the specification for claim 284 as defined in the instant application.

Case III describes treatment of a patient with cancer first by systemic administration compositions comprising phloretin (chemotherapeutic agent), cytotoxic drugs, DMSO and HA, then by administration both systemically and by direct injection compositions comprising phloretin (chemotherapeutic agent), cytotoxic drugs and HA. Hence the specification describes to the skilled addressee in the art a pharmaceutical composition comprising as a **first** component for systemic administration a formulation comprising HA and phloretin; and administration by injection of a second component a formulation comprising of HA.

Thus Case III provides support in the specification for claim 284 as defined in the instant application.

Case VI describes component 1 comprising various anti-cancer agents at various dosage amounts which were administered both systemically and directly by injection.

Case VIII describes systemic administration of component 1 comprising indomethacin (NSAID) and HA, and injection of component 2 comprising bleomycin (anti-cancer agent) and HA.

Case XXI describes both systemic administration and injection of component 1 comprising Oncostatin (anti-cancer agent) and HA; indomethacin and HA; and Vitamin C (anti-oxidant) and HA.

Thus these Cases provide support for a selection of components 1 and 2, at different dosage amounts, as defined in claim 284.

A summary of selected Cases in the specification in regard the specific components of the compositions which were administered to patients is provided in the **Table** below.

Case	Component 1	Component 2	Comment/result
I	Adriamycin (systemic and injection)	indomethacin	no apparent surviving tumour
	HA	HA	
II	HA (systemic)		Patient in Complete remission
	phloretin		
	HA (systemic)	HA (injection)	
	carboplatinum	Methotrexate	
III	Phloretin + DMSO(systemic)	Phloretin (injection)	Tumour reduced by >50%
		HA	

Case	Component 1	Component 2	Comment/result
	Cytotoxic drugs +DMSO (systemic)	Cytotoxic drugs (injection)	
	HA	HA	
V		Phloretin (injection)	Total tumour necrosis
		HA	
		carboplatinum	
		methotrexate	
VI	Various anti-cancer agents (systemic); at various doses	Various anti-cancer agents (injection); at various doses	Regression of disease by 50%
	HA; at various doses	HA; at various doses	
VIII	Indomethacin (systemic)	Bleomycin (injection)	Patient in remission
	HA	HA	
XIB	Carboplatin (systemic)	Methyl CCNU (injection)	Patient in Complete remission
	HA	carboplatin	
		methotrexate	
	Phloretin	HA	
	HA		
	methotrexate		
	HA		
			Patient in remission
XVII	5FU		
	mitomycin		
	novantrone		
	HA		
	Vitamin C		
XVIII	Vitamin C		Patient improved
	HA		
	Indomethacin		

Case	Component 1	Component 2	Comment/result
	(NSAID)		
	HA		
XXI	Oncostatin (systemic)	Oncostatin (injection)	Regression of tumour
	HA	HA	
	Vitamin C	Vitamin C	
	HA	HA	
	indomethacin	indomethacin	
	HA	HA	
XXII	Oncostatin (systemic)	Oncostatin (injection)	Reduction in tumour
	HA	HA	
	indomethacin	indomethacin	
	HA	HA	
	Vitamin C	Vitamin C	
	HA	HA	
XXXI	Phloretin (systemic)	Phloretin (injection)	Excellent response to NSAID and HA; no side effects
	Vitamin C	Vitamin C	
	HA	HA	
	naproxen	naproxen	
	indomethacin	indomethacin	

Applicant respectfully submits that the above Cases clearly provide support in the description for the present claims and respectfully request reconsideration.

2. Claims 284-286 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject

matter which applicant regards as the invention, as set forth in the previous Office action.

> The Examiner states, "Applicant's arguments filed March 6, 2006 have been fully considered but they are not persuasive. Applicant presents definitions of (1) "chemotherapeutic drug," (2) "anti-cancer drug" and (3) "drug suitable to treat cancer." Applicant does not present any evidence that one of ordinary skill would be apprised of the metes and bounds of these categories, particularly "drug suitable to treat cancer." Applicant defines such drugs as "molecules that may not be cytotoxic but could be used in combination with cytotoxic agents to produce slowing, regression or eradication of cancer." This definition would appear to include any pharmaceutically acceptable excipient for the administration of "anti-cancer drugs" or "chemotherapeutic drugs" and is much more broad than one of ordinary skill would surmise without having this particular definition. This definition is not in the specification. Further regarding "chemotherapeutic drugs," when such drugs are described in the specification, they are drawn only to those having well-known utility in treating cancer.".

Applicant respectfully disagrees. In the light of use of different components and dosages as discussed above, there appears to be sufficient support for generic terms defined in claim 284. Further, terms such as NSAID, anti-cancer agents, chemotherapeutic agents and anti-oxidants find support in the specification or are well known in the art to the skilled addressee. For example, *NSAIDs* include indomethacin and naproxen [*para 0093*]. *Chemotherapeutic agents* are chemicals that are used in the treatment or control of diseases caused by pathogenic-invading organisms or cells (*Korolkovas, "Essentials of Medicinal Chemistry, 2nd ed 1988; Part IV, p 571).* Chemotherapeutic agents include anti-cancer agents or drugs suitable for use to treat cancer. Examples of chemotherapeutic agents include novantrone (Mitoxantrone), methotrexate, 5-FU (5-Fluorouracil), carboplatinum, methyl CCNU and mitomycin C [*para 100*]. Other chemotherapeutic agents would be known to the skilled addressee in the art. *Anti-oxidants* are substances capable of inhibiting oxidation and include ascorbic acid, Vitamin C (*Korolkovas, "Essentials of Medicinal Chemistry, 2nd ed 1988; p1112).* Applicant respectfully requests reconsideration.

3. Claims 284-286 are again rejected under 35 U.S.C. 103(a) as being unpatentable over DELLA VALLE et al (US 5,166,331) in view of FRANCHI et al (Rec. Prog. Med., 1989 – abstract) and WOOD (US 4,912,136), as set forth in the previous Office action.

> The Examiner states, "Applicant's arguments filed March 6, 2006 have been fully considered but they are not persuasive.
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> It appears to be Applicant's position that Della Valle discloses only that which is set forth in the claims of the Della Valle patent and does not address that which was cited in the action other than repeating it. Applicant further argues in a piecemeal manner that neither Franchi nor Wood mention HA or the treatment of cancer. However, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references.
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> See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).
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> Regarding Applicant's intended use, the treatment of cancer, intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In this case, this intended is not recited in the claims.".

Della Valle putatively discloses HA of MW of about 500-730 kDa and suggests that HA is a suitable vehicle for delivery of a variety of pharmaceutical agents, including NSAIDs and chemotherapeutics. Hence *Della Valle* teaches use of HA only in the delivery of agents, and not the use of HA as a drug. The examples of the present application (particularly Case III) provide a clear benefit for HA over simple delivery agents such as DMSO. Further, in *Della Valle*, there is neither an indication of a dosage form used as a combination of HA and another drug, nor a suggestion, motivation or direct teaching of any form of therapeutic advantage for the use of HA for drug delivery.

Thus, *Della Valle* neither discloses or teaches or even alludes to either the **combination** of pharmaceutical compositions or the dosage forms as defined in the instant claims.

Franchi only teaches the treatment of rheumatoid arthritis by intra-articular administration of methotrexate and orgotein (an antioxidant), according to the abstract. HA is neither disclosed nor taught in this abstract.

Wood only teaches the use of NSAID. HA is neither disclosed nor taught in this patent. The inventors acknowledge use of NSAIDs, particularly indomethacin. However, using these drugs alone produces prohibitive side effects in human subjects (*see para [0072] of instant application*). The combination of NSAID and HA constitute part of the essential elements of the present invention.

The present invention as defined in claims 284-286 relates *inter alia* to a specific **combination** of dosage forms. Further the first dosage is in a form of a **systemic** administration to a human and the second dosage is in form for **injection** into a human. Systemic administration includes formulations administered intravenously, intra-arterially, intra-peritoneally, intra-pleurally, trans-dermally, topically, rectally, orally or by direct injection.

Clearly, as noted by the Examiner, none of the prior art documents discloses or teaches this combination of dosage forms. Furthermore, the combined mode of administration is not disclosed nor taught in the prior art.

Moreover, there is no motivation, in any of the prior art cited by the Examiner, either separately or as a combination, to try the combination of pharmaceutical compositions, the specific dosage forms and the combined mode of delivery as defined in the present invention with an expectation of success.

Therefore, we respectfully submit that the invention as defined in claims 284-286 is inventive and patentable. Applicant respectfully requests reconsideration.

If there any questions regarding this Amendment or the application in general, a telephone call to the undersigned would be appreciated since this should expedite the prosecution of the application for all concerned.

If necessary to effect a timely response, this paper should be considered as a petition for an Extension of Time sufficient to effect a timely response, and please charge any deficiency in fees or credit any overpayments to Deposit Account No. 04-1105.

Respectfully submitted,

Date: July 20, 2006

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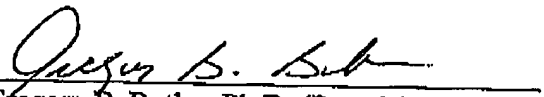

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